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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/719,017	03/05/2001	Jerome Pierrard	PH-98/032	3131

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SLOBODYANSKY, ELIZABETH

ART UNIT	PAPER NUMBER
1652	17

DATE MAILED: 04/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)
	09/719,017	PIERRARD ET AL.
	Examiner Elizabeth Slobodyansky	Art Unit 1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 06 February 2003.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 21-37 and 39-44 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 21-37 and 40-43 is/are rejected.
- 7) Claim(s) 39 and 44 is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>13</u> . | 6) <input type="checkbox"/> Other: _____. |

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DETAILED ACTION

The amendment filed February 6, 2003 canceling claim 38 and amending claims 21-23, 39, 43 and 44 has been entered.

Claims 21-37 and 39-44 are pending.

Information Disclosure Statement

In response to Applicant's request (Remarks, page 3), the examiner confirms that the initialed references on form PTO-1449 were considered by the examiner.

Specification

The instant disclosure contains sequence disclosure that is encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. 37 CFR 1.821(d) requires the use of assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences. For example, on page 22, line 9, the sequence of more than ten nucleotides is recited without a sequence identifier or reference to the sequence of which it is a fragment.

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Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a provisional rejection that would apply over specific embodiments ('suitable system') of the invention if they were claimed. Such embodiments are non-obvious.

The rejection would be made with regard to the deposit of pRPA-BCAT4 and derivative plasmids. The grounds for such rejection were explained in the Office action mailed September 30, 2003.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 21, with dependent claims 22-37 and 39-42, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 recites the limitation "the industrial process". It is unclear what is the essential property that makes the process "industrial". The definition given in the specification is vague as referring to the term. as "generally" which does not exclude

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other meanings. Furthermore, it defines the term by non-limiting examples (page 10, lines 4-14).

The term "high" in claim 24 is a relative term which renders the claim indefinite. The term "high" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. A density of biomass would differ for different expression systems. Neither the specification nor the art define the density of biomass that is considered to be "high" for *E. coli* strain W comprising a P_{trp} promoter. Further, the degree of expression of heterologous proteins depends depend on many factors such as the nature of the protein, for example.

Claim 41 is unclear. It depends from claim 40 that is limiting a heterologous protein to an enzyme. Claim 41 is limiting the enzyme that "is useful for the biocatalysis of chemical reactions. Since enzymes by definition are "useful" for the biocatalysis of chemical reactions. Amending claim 41 to recite "wherein the enzyme is further used for the biocatalysis of chemical reaction", for example, would obviate this rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be

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patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 21-28, 33-37, 40, 41 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cambiaghi et al. in view of Makrides et al.

Cambiaghi et al. (US Patent 5,424,196, form PTO-1449 filed December 7, 2000, reference AD) teach the use *E. coli* strain W (ATCC 9637) for the expression of a heterologous enzyme, GI-7-ACA acylase, (columns 15-17, Example 9). They teach that *E. coli* strain W (ATCC 9637) has high level of GI-7-ACA acylase productive capacity (column 17, lines 46-48). They teach a derivative of *E. coli* strain W (ATCC 9637) selected by clonal selection and genetic manipulation. They teach sources of nitrogen such as yeast extract (column 17, lines 55-60).

Makrides et al. (form PTO-892 mailed September 30, 2002) review strategies for high-level expression of heterologous genes in *E. coli*. They teach advantages of various promoters including P_{trp} promoter (pages 513-514). They teach fermentation strategies (page 525).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use any strain of *E. coli* transformed with a DNA encoding a heterologous protein under control of any known promoter reviewed by Makrides et al., including P_{trp} promoter, to produce a heterologous protein.

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It would have been further obvious to one of ordinary skill in the art at the time the invention was made to use optimal conditions for fermenting *E. coli* transformed with a DNA encoding a heterologous protein under control of the P_{trp} promoter. *E. coli* is the most studied and widely used host system for these purposes and the various conditions for its fermentation are known in the art. Absent unexpected results, various conditions are matter of choice.

Claims 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cambiaghi et al. in view of Makrides et al. and further in view of Lee et al.

The teachings of Cambiaghi et al. and Makrides et al. are outlined above.

Lee et al. (form PTO-1449 filed December 7, 2000) teach high density cultivation of *E. coli* strain W using sucrose as a carbon source (page 971, introduction).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use sucrose as a carbon source for optimal fermentation conditions of *E. coli* strain W.

Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cambiaghi et al. in view of Petre et al.

The teachings of Cambiaghi et al. are outlined above. They teach the use of *E. coli* strain W for the production of GI-7-ACA acylase.

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Petre et al. (US Patent 5,635,391, form PTO-892 mailed September 30, 2002) teach expression of a heterologous nitrilase, the nitrilase from *Comamonas testosteroni* sp., in *E. coli* TG1 under control of the P_{trp} promoter linked to the ribosome binding site of the λ phage CII gene (RBSCII) (Example 5, column 11, line 36, through column 13, line 64, especially column 12, lines 30-32, claims 1, 6-8).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to express the *Comamonas testosteroni* sp. nitrilase in another strain of *E. coli*, such as *E. coli* strain W, as a matter of convenience and/or choice.

Allowable Subject Matter

Claims 39 and 44 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Response to Arguments

Applicant's arguments filed February 6, 2003 have been fully considered but they are not persuasive.

With regard to the biological deposit, *supra*, Applicants argue that "plasmid pRPA-BCAT4 and derivative plasmids are readily available to the public". As evidence of such public availability, Applicants refer to the description of said plasmid in "U.S.

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Patent No. 6,180,359, in Example 2 and Figure 3" (Remarks, page 3). Even if the Declaration by Dr. Jerome Pierrard filed on December 21, 1999 in 08/957,621 (issued as US Patent 6,180,359) regarding the deposit of pRPA-BCAT3 would apply to the plasmids of the instant invention, it does not control the instant application. The declaration should be filed separately in each case when it is required.

With regard to the 112, 2nd rejection, the examiner disagree with Applicants position that volume of two liters renders the process industrial (page 4). Volumes of two liters and more are often used in the laboratory settings. With regard to the term "high", the examiner disagree with Applicants' statement that Makrides et al. provide art accepted definition of "high density of biomass". Makrides et al. explain that the disclosed "methods can achieve cell concentration in excess of 100 g (dry cell weight)" without defining the metes and bounds of the term (page 525, last paragraph).

With regard to claim 41, the rejection was reworded and is responsive to the arguments on page 6.

With regard to the art rejections, Applicants argue that "Cambiaggi et al. does not disclose or suggest the use of the P_{tp} promoter in conjunction with *E. coli* strain W for production of heterologous proteins" (page 8). The examiner agrees with that. However, the Cambiaggi et al. is applied under 103(a) not 102(b) and, therefore should not disclose the same invention but only should make it obvious. Applicants continue "Makrides et al. does not disclose *E. coli* strain W or suggest any promoters or

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fermentation conditions that would produce high levels of heterologous proteins in that strain of *E. coli*" (page 8). This is not persuasive because Makrides et al. suggest the use of any disclosed promoter in any strain of *E. coli* to produce high levels of heterologous proteins. Absent unexpected results, any strain comprising any promoter is useful for that purpose. Further, Applicants did not show that any heterologous protein will be expressed at a higher level in *E. coli* strain W comprising P_{trp} promoter compared with other *E. coli* strains. They disclose results of expression of two genes, NitB and PAMII polyamidase, in *E. coli* strains W, DH5a and BL21. For each of two genes, the expression in *E. coli* strain W is higher than in strains DH5a and BL21. However, the ratio of expression among three strains is different in two disclosed cases. For PAMII polyamidase, the difference is much smaller between *E. coli* strain W and *E. coli* strain BL21 than between *E. coli* strains BL21 and DH5a (page 21, Table 1 and page 24, Table 2). The claims are drawn to the expression of an enormous number of heterologous proteins. It is unpredictable whether another protein, let alone any protein, will be produced at a higher level in a *E. coli* W strain. However, unexpected results, if they are shown, must be commensurate in scope with claimed invention.

Applicants argue that there is "no disclosure or suggestion in Petre et al. to substitute the nitrilase with any other enzyme, let alone substitute it with an acylase" (page 11). This is not persuasive because the disclosure of Petre et al. differs from the invention of claim 42 only in that another strain of *E. coli*, *E. coli* TG1, is used as a host

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cell. Petre *et al.* do not teach that *E. coli* TG1 was chosen for any particular reason other than availability at a particular time and place. This suggests its substitution with any strain of *E. coli*, including strain of *E. coli*, *E. coli* W, used as a host cell by Cambiaghi *et al.*

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

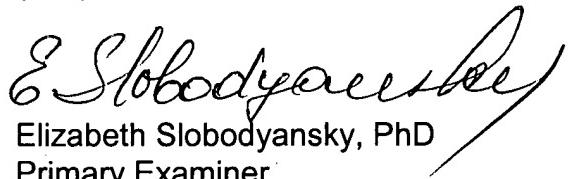
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.


Elizabeth Slobodyansky, PhD
Primary Examiner

April 15, 2003